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EXAMINER
LU, FRANK WEI MIN

ART UNIT	PAPER NUMBER
1634	26

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/402,277	Applicant(s) Kawashima et al.,
	Examiner Frank Lu	Art Unit 1634

-- ***The MAILING DATE of this communication appears on the cover sheet with the correspondence address*** --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 11, 2002*.

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-26, 59-64, and 67-73* is/are pending in the application.

4a) Of the above, claim(s) *59-64* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-26 and 67-73* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office action filed on October 11, 2002 has been entered as Paper No: 25. The claims pending in this application are claims 1-26, 59-64, and 67-73 with claims 59-64 withdrawn from consideration as the result of the restriction requirement.

Election/Restriction

2. This application contains claims 59-64 drawn to an invention nonelected with traverse in Paper No. 17. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.0

Drawings

3. The proposed drawing correction of Figure 3 has been approved by the examiner. Applicant is required to submit a proposed drawing correction in reply to this Office action. Note that the specification only describes Figure 3 and the proposed drawing correction of Figure 3 contains Figures 3A and 3B. Appropriate correction in the specification is required.

Claim Objections

4. Claim 1 is objected to because of the following informalities: there should be a "and " between two "wherein" phrases.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1, 2, 4, 6-26, and 67-73 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Note that claims 2, 4, 6-26, and 67-73 are dependent on claim 1.

7. Claim 1 is rejected as vague and indefinite because it is unclear what it intended. Since step E) is optional and the phrases "wherein said first nucleic acid sequence hybridizes to one of said plurality of primers and said second nucleic acid sequence is complementary to a sequence which hybridizes to one of said plurality of primers" and "wherein said first and second nucleic acid sequences are provided at the 3' and 5' ends of said single-stranded target nucleic acid molecule" are after step E) in the claim, it is unclear whether these phrases are optional or not. Please clarify.

8. Claim 6 is rejected as vague and indefinite because it is unclear when a tag is ligated into the given nucleic acid sequence. If the tag is ligated into the given nucleic acid sequence before an amplification reaction, the tag can not be used to identify the amplification product since there is no tag in the amplification products. Please clarify.

9. Claims 23-26 and 69 are rejected as vague and indefinite because it is unclear what it intended. Since claim 1 has a single stranded target nucleic acid molecule comprising a given

nucleic acid sequence while claims 23-26 and 69 are directed to amplify a plurality of different given nucleic acid sequence, claims 23-26 and 69 lacks insufficient antecedent basis.

10. Claim 26 is rejected as vague and indefinite because claim 26 lacks insufficient antecedent basis since "different given nucleic acid" in claim 23 appears to be different from "said different nucleic acid" in claim 26. Please clarify.

11. Claim 72 is rejected as vague and indefinite because it is unclear how many the given nucleic acid sequence is in each target nucleic acid molecule. The phrase "primers suitable for amplifying the given nucleic acid sequence which said molecule comprises, then amplifying the target nucleic acid molecules, and hence the given nucleic acid sequences" is unclear since this phrase suggests that each target nucleic acid molecule can have one given nucleic acid sequence or more than one target nucleic acid molecules. From this phrase, it is also unclear whether the method in claim 72 amplifies partial nucleic acid molecule (the given nucleic acid sequence) or amplifies whole nucleic acid molecule. Please clarify.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was

commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1, 2, 4, 6-9, 11-22, 67, 68, and 71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adams *et al.,* (WO 96/04404, published on February 15, 1996) in view of Deugau *et al.,* (US Patent No. 5,508,169, published on April 16, 1996).

Regarding claims 1, 2, 4, 6-9, 14-18, 22, 67, and 71, as shown in Figures 2A to 2L, Figure 3, and example 3, Adams *et al.,* taught a method for performing amplification of nucleic acid on supports. In this method, a target nucleic acid (first nucleic acid in this reference) hybridized with one or more of plurality of identical primers recited in claim 7 (second nucleic acid in this reference, see last paragraph in page 25) that had a sequence complementary to the target sequence and was covalently linked to the support, and then PCR (denaturation at 94 ^{0}C as recited in claim 15, annealing at 55 ^{0}C and extension at 75 ^{0}C) was performed using the target nucleic acid as a template in the presence of thermostable polymerase, enzyme buffer, labeled such as p^{32} labeled and unlabeled dNTP in an automated instrument as recited in claims 6, 14-18, 22, and 71 (see third paragraph of page 18 and second paragraph of page 24). During the PCR cycles (for example, 30 cycles, see example 2 in page 24), the amplified products from the early cycles were annealed with different sets of identical primers in latter cycles as recited in steps D) and E) of claim 1 and steps F) and G) of claims 2 and 67 (see pages 5-7 and 17-26).

Adams *et al.,* also taught that two different types of primer were immobilized on a support. For example, as shown in Figure 1B, a target double stranded nucleic acid (first nucleic acid 23 in this patent) comprised a first strand 25 and a second strand 27 and each strand had two target sequences a and b at their 3' and 5' ends recited in claim 5. Second nucleic acid 13 (primer) was complementary to target sequence a of strand 25 and third nucleic acid 15 (primer) was complementary to sequence b of strand 27 (both second and third nucleic acids were immobilized on a support and served as primers) (see pages 14-17 and Figures 1A to 1M). Note that: (1) if n was equal to 1 in claim 9, plurality of primers equal to 2 as recited in claims 8 and 9 which was taught by Adams *et al.,* (2) in Figure 1G, a and b of the first strand 25 was considered as the first nucleic acid sequence that hybridized with primer 13 and the second nucleic acid sequence that hybridized with a sequence (31) recited in claim 1; and (3) since third nucleic acid 15 (primer) was complementary to sequence b of strand 27 and the first strand 25 and the second strand 27 were plus and minus strands of target double stranded nucleic acid (first nucleic acid 23), sequence b of strand 25 should be identical to third nucleic acid 15 (primer) as recited in claim 4.

Regarding claim 11, the different primers had about the same concentrations (see example 2, page 24, last paragraph).

Regarding claims 12 and 13, the primers were homogeneously dispersed over a given area and be located in a predetermined arrangement (see Example 6, page 28, second paragraph).

Regarding claims 19-21, PCR products amplified with primers with a restriction endonuclease site were released by cleavage with the restriction endonuclease(see pages 32 and 33).

Adams *et al.,* do not disclose to ligate the first and second nucleic acid sequence to the given nucleic acid sequence as recited in claims 1 and 68 (here a target nucleic acid includes first and second nucleic acid sequence and the given nucleic acid sequence).

Deugau *et al.,* teach to ligate the first and second nucleic acid sequence to the given nucleic acid sequence (see Figure 3). Indexing linkers were considered as the first and second nucleic acid sequence here.

Therefore, in the absence of an unexpected result, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have synthesized a target nucleic acid comprising first and second nucleic acid sequence and the given nucleic acid sequence in view of prior art of Adams *et al.,* and Deugau *et al.*. One having ordinary skill in the art would have been motivated to modify the method of Adams *et al.,* because the ligation of indexing linkers (the first and second sequences here) to a nucleic acid fragment (a given nucleic acid sequence here) would help selective isolation, identification, amplification, labeling, and modification, of nucleic acid fragments, especially subsets of such fragments released by cleavage using restriction endonucleases (see abstract of Deugau *et al.,*) and the simple replacement of a target nucleic acid from one preparation from a target nucleic acid from another preparation (IE., ligated nucleic acid) would have been, in the absence of an unexpected result, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their

expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

14. Claims 1, 2, 4, 6, 8-10, 12-24, 67-69, 71, and 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adams *et al.,* (US Patent No., 6,060,288, filed on February 14, 1997) in view of Deugau *et al.,* (US Patent No. 5,508,169, published on April 16, 1996).

Regarding claims 1, 2, 4, 8, 9, 14-18, 22, 67, and 71, as shown in Figures 2A to 2L, Figure 3 and example 1, Adams *et al.,* taught a method for performing amplification of nucleic acid on supports. In this method, a target nucleic acid (first nucleic acid in the patent) hybridized with one or more of plurality of primers that had a sequence complementary to the target sequence and was covalently linked to the support, and then PCR (denaturation at 94^0 C as recited in claim 15, annealing at 55^0 C and extension at $75\ ^0$C) was performed using the target nucleic acid as a template in the presence of thermostable polymerase, enzyme buffer, labeled such as p^{32} labeled and unlabeled DNTP in an automated instrument as recited in claims 6, 14-18, 22, and 71 (see columns 10 and 22). During the PCR cycles (for example, 30-100 cycles, see example 2 in columns 22 and 23), the amplified products from the early cycles were annealed with different sets of identical primers in latter cycles as recited in steps D) and E) of claim 1 and steps F) and G) of claims 2 and 67 (see column 1-3 and 10-12).

Adams *et al.,* also taught that two different types of primer were immobilized on a support. For example, as shown in Figure 1B, a target double stranded nucleic acid (first nucleic acid 23) comprised a first strand 25 and a second strand 27 and each strand had two target sequences a and b at their 3' and 5' ends recited in claim 5. Second nucleic acid 13 (primer) was complementary to target sequence a of strand 25 and third nucleic acid 15 (primer) was complementary to sequence b of strand 27 (both second and third nucleic acids were immobilized on a support and served as primers) (see column 8-10 and Figures 1A to 1M). Note that: (1) if n was equal to 1 in claim 9, plurality of primers equal to 2 as recited in claims 8 and 9 which was taught by Adams *et al.,* (2) in Figure 1G, a and b of the first strand 25 was considered as the first nucleic acid sequence that hybridized with primer 13 and the second nucleic acid sequence that hybridized with a sequence (31) recited in claim 1; and (3) since third nucleic acid 15 (primer) was complementary to sequence b of strand 27 and the first strand 25 and the second strand 27 were plus and minus strands of target double stranded nucleic acid (first nucleic acid 23), sequence b of strand 25 should be identical to third nucleic acid 15 (primer) as recited in claim 4.

Regarding claim 10, multiplex amplification of nucleic acids from different organisms required a plurality of different primers (see column 5).

Regarding claims 12 and 13, the primers were homogeneously dispersed over a given area and be located in a predetermined arrangement (see Example 3, example 3, column 23).

Regarding claims 19-21, PCR products amplified with primers with a restriction endonuclease site were released by cleavage with the restriction endonuclease(see column 26).

Regarding claims 23, 24, 69, and 72, Adams *et al.,* taught multiplex PCR in the presence of plurality of different target nucleic acid sequences and plurality of primer (see columns 3-5).

Adams *et al.,* do not disclose to ligate the first and second nucleic acid sequence to the given nucleic acid sequence as recited in claims 1 and 68 (here a target nucleic acid includes first, second nucleic acid sequence and the given nucleic acid sequence).

Deugau *et al.,* teach to ligate the first and second nucleic acid sequence to the given nucleic acid sequence (see Figure 3). Indexing linkers were considered as the first and second nucleic acid sequence here.

Therefore, in the absence of an unexpected result, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have synthesized a target nucleic acid comprising first and second nucleic acid sequence and the given nucleic acid sequence in view of prior art of Adams *et al.,* and Deugau *et al.*. One having ordinary skill in the art would have been motivated to modify the method of Adams *et al.,* because the ligation of indexing linkers (the first and second sequences here) to a nucleic acid fragment (a given nucleic acid sequence here) would help selective isolation, identification, amplification, labeling, and modification, of nucleic acid fragments, especially subsets of such fragments released by cleavage using restriction endonucleases (see abstract of Deugau *et al.,*) and the simple replacement of a target nucleic acid from one preparation from another target nucleic acid (IE., ligated nucleic acid) would have been, in the absence of an unexpected result, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

15. Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Adams *et al.,* (1997) in view of Deugau *et al.,* (1996) as applied to claims 1, 2, 4, 8-10, 12-24, 67-69, 71, and 72 above, and further in view of Schumn *et al.,* (US Patent No., 5,843,660, filed on April 15, 1996).

The teachings of Adams *et al.,* (1997) and Deugau *et al.,* have been summarized previously, *supra.* Adams *et al.,* teach to incorporate a fluorescence label into a amplification product (see column 4).

Adams *et al.,* and Deugau *et al.,* do not disclose to use different fluorescent tags in order to distinguish different amplified products as recited in claim 26.

Schumn *et al.,* do teach to use different fluorescent tags in order to distinguish different amplified products. For example, see column 3, Examples 19 and 20 in column 29 and Figures 19 and 20.

Therefore, in the absence of an unexpected result, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed multiplex PCR using different target nucleic acids as templates in the presence of different fluorescent tags in view of the patents from Adams *et al.,* Deugau *et al.,* and Schumn *et al.*. One having ordinary skill in the art would have been motivated to modify the method recited in claim 1 in order to distinguish different amplified products because Schumn *et al.,* suggested that different fluorescent tags in multiplex PCR were used to distinguish different amplified products (see column 3). One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to distinguish different amplified products using different fluorescent tags.

16. Claim 70 is rejected under 35 U.S.C. 103(a) as being unpatentable over Adams *et al.,* (1997) in view of Deugau *et al.,* (1996) as applied to claims 1-6, 8-10, 12-24, 67, 68, and 71 above, and further in view of Pease *et al.,* (Proc. Nat. Acad. Sci. USA, 91, 5022-5026, May 1994).

The teachings of Adams *et al.,* (1997) and Deugau *et al.,* have been summarized previously, *supra.*

Adams *et al.,* and Deugau *et al.,* do not disclose to arrange a plurality of primers in a grid pattern on a solid support as recited in claim 71.

Pease *et al.,* do teach to arrange a plurality of primers in a grid pattern on a solid support (see Figure 5B in page 5026).

Therefore, in the absence of an unexpected result, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have arrange a plurality of primers in a grid pattern on a solid support in view of prior art of Adams *et al.*, Deugau *et al.*, and Pease *et al.*, One having ordinary skill in the art would have been motivated to modify the method as recited in claim 1 because the simple replacement of one primer formation pattern on a solid support from another primer formation pattern on a solid support (IE., grid pattern) would have been, in the absence of an unexpected result, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Response to Arguments

17. Applicant's arguments with respect to claims 1-26 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

19. No claim is allowed.

20. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703) 308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (703) 305-1270. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the patent Analyst of the Art Unit, Ms. Chantae Dessau, whose telephone number is (703) 605-1237.

Frank Lu
December 24, 2002

Ethan Whisenant
Primary Examiner